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BRIEF REPORT

Once-monthly oral ibandronate compared with weekly oral alendronate in postmenopausal osteoporosis: results from the head-to-head MOTION study

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ABSTRACT

Objective: Oral ibandronate 150 mg is the first bisphosphonate approved for once-monthly treatment of postmenopausal osteoporosis. To investigate whether once-monthly ibandronate 150 mg increases lumbar spine and total hip bone mineral density (BMD) to the same degree as weekly alendronate 70 mg.

Research design and methods: This was a 12-month, randomised, multinational, multicentre, double-blind, double-dummy, parallel-group, non-inferiority trial, conducted in 65 centres in North America, Latin America, Europe and South Africa. The study included postmenopausal women, mean lumbar spine (L2–L4) BMD T-score < -2.5 and ≥ -5.0. Patients received either ibandronate 150 mg once monthly or alendronate 70 mg once weekly.

Main outcome measures: Co-primary efficacy endpoints were 12-month change (%) from baseline in mean lumbar spine and total hip BMD. Changes (%) from baseline in trochanter and femoral neck BMD were also evaluated. Adverse events were monitored throughout. Once-monthly ibandronate was considered non-inferior to weekly alendronate if the lower boundary of the one-sided 97.5% confidence interval (CI) (or two-sided 95% CI) was $\geq -1.41\%$ for lumbar spine and $\geq -0.87\%$ for total hip.

Results: Mean relative 12-month changes were 5.1% and 5.8% (95% CI for difference, –1.13, –0.23) in lumbar spine and 2.9% and 3.0% (95% CI for difference, –0.38, 0.18) in total hip BMD with once-monthly ibandronate and weekly alendronate, respectively; meeting the non-inferiority criteria at both sites. Gains in trochanter and femoral neck BMD were similar with both treatments. Both regimens were well tolerated.

Trial registration: The MOTION study is registered with the International Federation of Pharmaceutical Manufacturers and Associations trial portal, under the ID number MM17385.

Conclusions: Once-monthly ibandronate was shown to be clinically comparable to weekly alendronate at increasing BMD after 12 months in both the lumbar spine and total hip.

Introduction

Oral bisphosphonates are the current mainstay of treatment for postmenopausal osteoporosis as a result of their established efficacy in terms of bone mineral density (BMD) gains, fracture risk reduction, and good safety and tolerability[1–9]. At the time of this study, two bisphosphonates – alendronate and risedronate – were available as once-weekly oral formulations, while oral ibandronate 150 mg was the only bisphosphonate

approved for once-monthly administration. Studies have demonstrated that the reduced dosing frequency of once-monthly ibandronate is preferred by patients over a weekly alendronate regimen[10] and has resulted in better persistence with medication compared with weekly bisphosphonates[11,12]. A 2-year study has shown that improved adherence to bisphosphonate therapy is associated with significantly fewer fractures[13].

MOTION (Monthly Oral Therapy with Ibandronate for Osteoporosis iNtervention) is the first head-to-head study comparing the efficacy of once-monthly ibandronate with weekly alendronate in women with postmenopausal osteoporosis. Low BMD is a strong predictor of fracture risk and pharmacological increases in BMD are associated with fracture risk reduction[14,15]. Bisphosphonate-associated increases in BMD are accepted as an established surrogate for fracture risk reduction[14,15]. The primary aim of MOTION was to investigate whether monthly ibandronate 150 mg could increase BMD at the lumbar spine and total hip, to the same degree as weekly alendronate 70 mg after 12 months of treatment. Continuous assessment of the tolerability and safety of both regimens was also completed. Weekly alendronate was chosen as the active comparator as it has previously demonstrated larger increases in BMD and reduction of bone turnover compared with risedronate[16], and has demonstrated significant fracture risk reduction[1,2].

Patients and methods

Study participants

Patients were postmenopausal women (age 55–84 years, ≥5 years since menopause), with mean lumbar spine (L2–L4) BMD T-score <–2.5 and ≥–5.0. Patients were required to be ambulatory at the study start, and not expected to be hospitalised, immobilised or bedridden before completion. Key exclusion criteria included significant medical disease, inability to stand or sit upright for 60 min, hypersensitivity to bisphosphonates or to any of the excipients contained in the tablets, contraindications for calcium or vitamin D therapy, renal impairment (GFR <30 ml/min), history of major upper gastrointestinal disease, any active disease known to influence bone metabolism, or recent treatment with drugs known to affect bone metabolism. All participants gave written informed consent.

Study design

MOTION was a 12-month, randomised, multicentre, double-blind, double-dummy, parallel-group, non-inferiority trial conducted at 65 centres in North America, Latin America, Europe and South Africa. Patients were randomised to receive ibandronate 150 mg monthly or alendronate 70 mg weekly. The study was conducted in accordance with the principles of the Declaration of Helsinki or with the laws and regulations of the country concerned, whichever provided greater protection to the individual. The study protocol was also approved by the appropriate institutional and ethical review boards.

To minimise the possible imbalance in distribution between groups, randomisation was stratified by country, history of clinical fractures and baseline total hip BMD T-score (≥–2.5, <–2.5). All patients received vitamin D 400 IU/day and elemental calcium 500 mg/day (upper limit 1500 mg/day) as dietary supplements throughout the study, irrespective of dietary intake. BMD was measured by a single DXA scan of the proximal femur and lumbar spine (mean BMD of at least two vertebrae [L2–L4]) at baseline and month 12.

Efficacy and safety evaluations

The co-primary efficacy endpoints were the 12-month relative change (%) from baseline in mean BMD of the lumbar spine and total hip. Assessment of mean change (%) from baseline at 12 months in trochanter and femoral neck BMD were secondary and exploratory endpoints, respectively. Other efficacy endpoints will be reported elsewhere (manuscript in preparation). Safety and tolerability were monitored throughout the study with the recording of clinical and laboratory adverse events.

Statistical analyses

The primary efficacy analysis was conducted on the per-protocol (PP) population, and confirmed in the intent-to-treat (ITT) population to evaluate the robustness of the results. ITT analysis can be associated with a higher standard deviation due to increased heterogeneity from 'non-conforming' patients. In a non-inferiority trial, high variation could falsely lead to the conclusion of no difference in the magnitude of effects between the treatment arms. This methodology is consistent with the recommendations provided by the European Regulatory Authority[17] and the extended Consolidated Standards of Reporting Trials (CONSORT) statement[18].

The ITT population included all randomised patients who had received at least one dose of trial medication and had at least one follow-up efficacy datapoint. The PP population comprised all patients in the ITT population who had no major protocol violations, including: baseline lumbar spine T-score ≥–2.5; previous or concomitant diseases that could potentially affect bone metabolism; treatment with any drug affecting bone before randomisation; vitamin D deficiency at screening;

lack of compliance with active medication; unconfirmed menopausal status for at least 5 years.

A non-inferiority test was used to assess the primary endpoint. For the primary efficacy analysis, once-monthly ibandronate was considered non-inferior to weekly alendronate if the lower boundary of the one-sided 97.5% CI was ≥ –1.41% for lumbar spine and ≥ –0.87% for total hip as specified in the protocol. Therefore, if the difference in BMD gains between alendronate and ibandronate was < 1.41 or < 0.87 at the lumbar spine or total hip, respectively, the difference would be considered irrelevant and ibandronate would be deemed non-inferior to alendronate. Outlining a clinically relevant margin or level of BMD difference in this way is commonplace in bridging studies of bisphosphonates when showing equivalence or non-inferiority of a less-frequent regimen to the daily regimen that has demonstrated antifracture efficacy. Analyses of a two-sided 95% CI are presented here; these provide a lower boundary equal to that of a one-sided 97.5% CI.

The MOTION study used a margin of 30% of the clinically relevant difference in BMD between alendronate 70 mg and placebo, relating to an earlier placebo-controlled study[19], which was agreed to be appropriate by the FDA. The two primary hypotheses were tested sequentially; the second hypothesis (total hip BMD) was tested only if the first (lumbar spine BMD) was met. An analysis of covariance was conducted on relative changes from baseline in lumbar spine and total hip BMD, controlling for countries and baseline total hip BMD.

The safety analysis included all patients who had at least one dose of study medication, whether or not withdrawn prematurely.

Results

Patient disposition and baseline characteristics

In total, 1760 patients were enrolled and randomised (weekly alendronate, *n* = 873; monthly ibandronate, *n* = 887; Figure 1). Treatment was received by 859 patients (98.4%) on alendronate and 874 patients (98.5%) on ibandronate. The study was completed by 771 patients (88.3%) and 775 patients (87.4%) in the alendronate and ibandronate arms, respectively. Reasons for study withdrawal (weekly alendronate vs. monthly ibandronate, respectively) included: adverse event (42 vs. 44); refused treatment (33 vs. 39); failure to return (6 vs. 7); failed inclusion or exclusion criteria (1 vs. 2); protocol violation (1 vs. 0); and 'other' (5 vs. 7).

The PP, ITT and safety populations comprised 1445, 1658 and 1733 patients, respectively. The demographic and baseline parameters were well-balanced between both treatment groups for all study populations (Table 1).

Efficacy

After 12 months, the relative changes in mean lumbar spine BMD (PP analysis) were 5.1 and 5.8% (95% CI for difference, –1.13, –0.23: non-inferiority condition met at ≥ –1.41) with once-monthly ibandronate and weekly alendronate, respectively (Figure 2; Table 2). The mean relative changes in total hip BMD (PP analysis) were 2.9 and 3.0% (95% CI for difference, –0.38, 0.18: non-inferiority condition

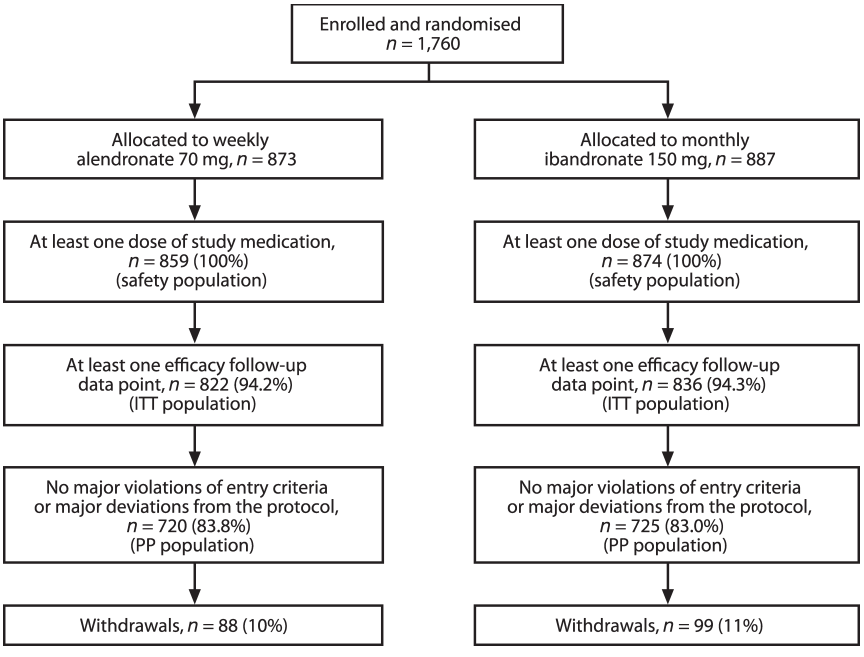

Figure 1. *Randomisation and patient flow*

Table 1. *Demographics and baseline characteristics (safety population)*

	Ibandronate 150 mg monthly (n = 874)	Alendronate 70 mg weekly (n = 859)
Age, mean (years)	65.6	65.6
Weight, mean (kg)	62.01	62.28
Height, mean (cm)	154.6	155.0
Caucasian (%)	83.3	80.8
Time since menopause, mean (years)	18.5	18.2
Previous fracture, mean (%)	39.0	38.2
Previous fracture since age 45, mean (%)	32.5	31.6
Lumbar spine (L2–L4) BMD, mean (T-score)	–3.238	–3.247
Total hip BMD, mean (T-score)	–1.730	–1.736

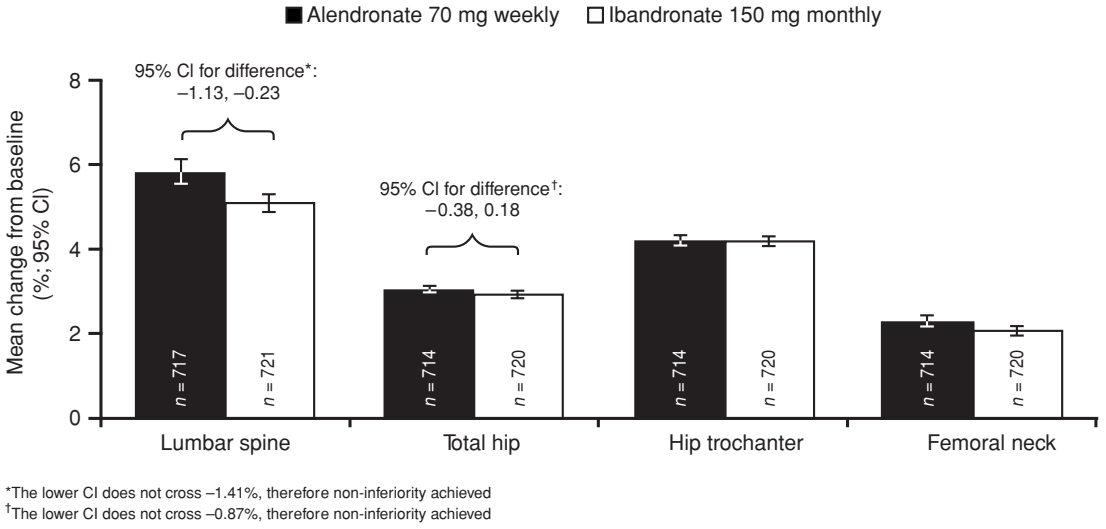

Figure 2. *Mean (%) change from baseline and 95% CI for between-group differences for lumbar spine and hip BMD (PP population)*

met at ≥–0.87) with once-monthly ibandronate and weekly alendronate, respectively (Figure 2; Table 2). All PP analyses were confirmed in the ITT population (relative change in lumbar spine BMD: 4.94 and 5.63% in the ibandronate and alendronate arms, respectively; 95% CI for difference, –1.12, –0.27: non-inferiority condition met at ≥–1.41%; relative change in total hip BMD: 2.84 and 2.98% in the ibandronate and alendronate arms, respectively; 95% CI for difference, –0.43, 0.10; non-inferiority condition met at ≥–0.87%).

After 12 months, the same gain in trochanter BMD was reported for both once-monthly ibandronate and weekly alendronate (4.2%, PP analysis; Figure 2). Comparable gains were also reported for femoral neck BMD: 2.1% with once-monthly ibandronate, 2.3% with weekly alendronate (PP analysis; Figure 2). All PP analyses were confirmed in the ITT population (relative change in trochanter BMD: 4.1 and 4.2% in the ibandronate and alendronate arms, respectively; relative change in femoral neck BMD: 2.0 and 2.2% in the ibandronate and alendronate arms, respectively).

Safety

The incidence of overall adverse events, drug-related adverse events, the most commonly represented body systems (GI disorders, cardiac disorders, infections and infestations) regardless of relationship to treatment, serious adverse events (related and unrelated to treatment), adverse events leading to withdrawal and deaths was similar across treatment groups (Table 3). All clinical fractures were reported as adverse events; the incidence was low and similar in both arms (Table 3). The incidence of vertebral

Table 2. *Mean baseline and 1-year follow up BMD, PP population (mean, SD)*

	Ibandronate 150 mg monthly	Alendronate 70 mg weekly
Lumbar spine (g/cm^2)		
Baseline	0.784 (0.076)	0.785 (0.077)
After 1 year	0.824 (0.082)	0.830 (0.083)
Change from baseline at 1 year	0.040 (0.033)	0.045 (0.034)
Total hip (g/cm^2)		
Baseline	0.773 (0.104)	0.778 (0.101)
After 1 year	0.796 (0.106)	0.802 (0.102)
Change from baseline at 1 year	0.022 (0.021)	0.023 (0.020)

Table 3. *Incidence of adverse events overall, and individual events occurring in ≥ 5% of patients (patients reporting at least one event)*

	Ibandronate 150 mg monthly (n = 874, %)	Alendronate 70 mg weekly (n = 859, %)
Overall adverse events		
All adverse events	659 (75.4)	632 (73.6)
All treatment-related adverse events	232 (26.5)	176 (20.5)
All serious adverse events	39 (4.5)	55 (6.4)
Serious treatment-related adverse events	1 (0.1)	5 (0.6)
Deaths	2 (0.2)	4 (0.5)
Adverse events occurring in ≥ 5% of patients, regardless of relationship to treatment		
Hypertension	68 (7.8)	51 (5.9)
Dyspepsia	60 (6.9)	48 (5.6)
Back pain	60 (6.9)	45 (5.2)
Arthralgia	47 (5.4)	49 (5.7)
Nasopharingitis	51 (5.8)	41 (4.8)
Influenza	49 (5.6)	36 (4.2)
Adverse events of special interest		
Osteoporotic fractures	18 (2.1)*	17 (2.0)
Vertebral	5 (< 1)	5 (< 1)
Non-vertebral	14 (1.6)	12 (1.4)
Musculoskeletal and general disorders†	59 (6.8)	26 (3.0)
Months 0–2	54 (6.2)	23 (2.7)
Months 3–12	11 (1.3)	4 (< 1)

*One patient experienced both a vertebral and non-vertebral fracture
†Includes events occurring within 3 days after dose administration and lasting no longer than 7days

osteoporotic fracture was 0.6% in each group and the incidence of non-vertebral osteoporotic fracture was 1.4 and 1.6% with alendronate and ibandronate, respectively. The incidence of events classified as musculoskeletal and general disorders (including influenza-like illness) occurring within 3 days after the dose and lasting no longer than 7 days was numerically greater with ibandronate (6.8 vs. 3.0% with alendronate), the incidence of influenza-like illness specifically was 3.2% with ibandronate and 0.7% with alendronate. As previously reported from earlier trials with monthly ibandronate, these events occurred early in the course of treatment, were self-limiting and did not require dose adjustment.

Discussion

In compliance with recommendations by ICH and other regulatory and health authorities[20–22], MOTION was designed and conducted as a non-inferiority study. The results show that once-monthly oral ibandronate achieved clinically comparable BMD gains, at the lumbar spine and total hip, compared with weekly alendronate in patients with postmenopausal osteoporosis. There were also comparable BMD improvements at the trochanter and femoral neck. Given that BMD is an accepted surrogate for fracture risk reduction, it may be assumed that similar antifracture efficacy is provided by both treatments. However, this would need to be confirmed in an appropriately designed, comparative study.

Previously, daily oral ibandronate 2.5 mg showed significant antifracture efficacy[8] with a 3-year vertebral fracture risk reduction of 62% vs. placebo ($p = 0.0001$) for a prespecified primary analysis using Cox regression (adjusted for possible inhomogeneities between treatment groups with respect to baseline BMD T-score above and below –2.0), and a reduction of 52% ($p = 0.0001$) in a secondary analysis without correction for the statistically significant interaction between treatment groups discovered after data unblinding in the primary analysis. In addition, although not observed in the overall population, non-vertebral antifracture efficacy was observed in a subgroup analysis of patients at higher risk (baseline femoral neck BMD T-score < -3.0)[8]. Once-monthly ibandronate (150 mg) was recently compared with this daily 2.5 mg regimen[9], and achieved superior BMD increases after 2 years of treatment at the lumbar spine ($p < 0.001$), as well as at the total hip, femoral neck and trochanter ($p < 0.05$).

Conclusion

In conclusion, the primary endpoint of MOTION was met, with once-monthly oral ibandronate shown to be as clinically effective as weekly oral alendronate for increasing BMD after 12 months in both lumbar spine and total hip in patients with postmenopausal osteoporosis. The two regimens also produced similar improvements in trochanter and femoral neck BMD after 12 months. Both treatments were generally well tolerated with monthly oral ibandronate and weekly alendronate shown to have very similar overall safety and tolerability profiles. The clinically comparable gains in BMD and similar safety profiles reported with once-monthly oral ibandronate and weekly alendronate confirm that monthly ibandronate is a useful treatment option for patients with postmenopausal osteoporosis.

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The MOTION study is registered through the International Federation of Pharmaceutical Manufacturers and Associations trial portal (IFPMA; http://www.ifpma.org/clinicaltrials.html). The Unique ID is MM17385.

Previous presentations of data from the MOTION study:

Abstracts W354, T383 and T377 at the 29th Annual Meeting of the American Society of Bone and Mineral Research (ASBMR 2007), Honolulu, USA, 16–19 September 2007.

References

1. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535-41
2. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077-82
3. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282:1344-52
4. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11:83-91

5. Schnitzer T, Bone HG, Crepaldi G, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. Aging (Milano) 2000;12:1-12
6. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344:333-40
7. Brown JP, Kendler DL, McClung MR, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int 2002;71: 103-11
8. Chesnut III CH, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004;19:1241-9
9. Miller PD, McClung MR, Macovei L, et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. J Bone Miner Res 2005;20:1315-22
10. Emkey R, Koltun W, Beusterien K, et al. Patient preference for once-monthly ibandronate versus once-weekly alendronate in a randomized, open-label, cross-over trial: the Boniva Alendronate Trial in Osteoporosis (BALTO). Curr Med Res Opin 2005;21:1895-903
11. Cooper A, Drake J, Brankin E. Treatment persistence with once-monthly ibandronate and patient support versus once-weekly alendronate: results from the PERSIST study. Int J Clin Pract 2006;60:896-905
12. Silverman SL, Chesnut III CH, Amonkar MM, et al. Improved persistence in women treated with once-monthly ibandronate versus weekly bisphosphonates: a first look. J Bone Miner Res 2006;21(Suppl 1):Abstract SU335
13. Siris ES, Harris ST, Rosen CJ, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc 2006;81:1013-22
14. Hochberg MC, Greenspan S, Wasnich RD, et al. Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. J Clin Endocrinol Metab 2002;87:1586-92
15. Wasnich RD, Miller PD. Antifracture efficacy of antiresorptive agents are related to changes in bone density. J Clin Endocrinol Metab 2000;85:231-6
16. Rosen CJ, Hochberg MC, Bonnick SL, et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. J Bone Miner Res 2005;20:141-51
17. International Conference on Harmonisation. Note for guidance on statistical principles for clinical trials (ICH-E9). 1998. http://www.emea.europa.eu/pdfs/human/ich/036396en.pdf. Accessed: October 2007
18. Piaggio G, Elbourne DR, Altman DG, et al. Reporting of noninferiority and equivalence randomized trials. An extension of the CONSORT statement. JAMA 2006;295:1152-60
19. Hosking D, Adami S, Felsenberg D, et al. Comparison of change in bone resorption and bone mineral density with once-weekly alendronate and daily risedronate: a randomised, placebo-controlled study. Curr Med Res Opin 2003;19:383-94
20. World Medical Association Declaration of Helsinki 2007. Ethical principles for medical involving human subjects. http://www.wma.net/e/policy/pdf/17c.pdf. Accessed: May 2007
21. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 2001. ICH harmonised tripartite guideline: choice of the control group and related issues in clinical trials (ICH-E10). http://www.fda.gov/cber/gdlns/clincontr0501.pdf. Accessed: May 2007
22. Surgeon General 2004 Bone Health and Osteoporosis: A Report of the Surgeon General. http://www.surgeongeneral.gov/library/bonehealth/. Accessed: June 2007

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